FALL 2017

BIOMEDICAL ENGINEERING

UNIVERSITY OF WISCONSIN-MADISON

ADVANCING TECHNOLOGIES FOR PERSONALIZED MEDICINE

Justin Williams

GREETINGS!

As we begin another academic year in Madison, it's my pleasure to reflect on just a few of the recent successes our department has seen in education, research, and entrepreneurship; and on the collaborative quality that links each of these accomplishments together.

BME's impact starts at the undergraduate level. In this newsletter, you'll read about just a few of our students' innovative solutions to the real-world problems posed to them in our unique, six-semester design program. I encourage you to explore more of the purposeful products created in these courses through our UW BME Design website (bmedesign.engr.wisc.edu/) and to stay tuned for the many future projects that will be created within our newly opened lab facilities. In addition to a new space dedicated to bio-instrumentation, with the help of generous donors, we were able to open two more lab spaces in early 2017. With nearly 2,500 square feet dedicated to design, fabrication and teaching, we have more than doubled the number of students that can fit within our walls.

It is through the exemplary, transdisciplinary work of our faculty that our students learn how to apply their knowledge in a diversity of environments. I am proud to work with leaders both within our department and across campus who are unafraid to look for answers in new places—it is only at UW-Madison that diagnosing genetic disorders with help from the School of Social Work, teaming up with neuroscientists to make a "thinking cap" a reality, and using the UW Arboretum's plant life as scaffolding for growing stem cells are all part of a normal day's work. Continued grants and recognition from national agencies, corporations, and foundations are proof that the community-minded approach that our department offers is exceptional in the greater scientific community.

Of course, all of these accomplishments and the others in this publication would not be possible without the incomparable support of our alumni; thank you for your continued dedication to this outstanding program.

SUPPORT BME !

To make a gift to the department, go to:

allwaysforward.org/giveto/bme

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Be sure to keep in touch via Facebook, Twitter, and LinkedIn and to stop by and say hello the next time you're in Madison!

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UW-Madison Biomedical Engineering Alumni and Current Members

Students can be seen working on a design project in the lab behind a plaque commemorating the work of department co-founders Willis Tompkins and John Webster.

Tompkins

Webster

BME FOUNDERS HONORED THROUGH PROMISE OF CONTINUED INNOVATION IN NEW LABS

BME pioneers, department founders, and now professors emeritus—combined, Willis Tompkins and John Webster's work in the field of engineering spans more than a century. This year, thanks to the help of generous donors, their legacy will continue to promote innovation in the form of two new lab spaces.

The Willis Tompkins & John Webster design spaces—comprised of a design studio and fab lab—opened in spring 2017 for student use. At more than 2,250 square feet, the updated area offers more than twice the working room of the department's former design labs.

"It is incredible to see how their legacy and innovation affected so many people," says John Puccinelli. As undergraduate advisor, Puccinelli will have the privilege of seeing students build on the solid foundation that Tompkins and Webster created for the department. In the semester since the opening of the labs, students from the department's six-semester design curriculum have already produced a diversity of healthcare solutions ranging from a therapeutic spider cage for individuals with musculoskeletal disorders to a sleep apnea therapy device.

Discover more undergraduate designs through the UW BME Design website: bmedesign.engr.wisc.edu/.

STUDYING THE HUMAN CONNECTOME TO INCREASE OUR UNDERSTANDING OF EPILEPSY

Francis Collins, the director of the National Institutes of Health, has called the human connectome "the symphony in our brain," played by electric circuit connections between its distinct functional regions.

Neurologic diseases can distort that intricate symphony—yet researchers still have a poor understanding of how that happens. In response, Collins launched the NIH Human Connectome Project in 2009 to map connections, or communication patterns, among the nerve cells in different areas of the brain, and invited research groups across the country to submit proposals.

Researchers at UW-Madison and the Medical College of Wisconsin in Milwaukee were successful in securing funding for not one, but two of those collaborative proposals: one for Alzheimer's disease and one for epilepsy. With software and technology development playing an especially important role in this field, the epilepsy project's co-principal investigator is Professor Elizabeth Meyerand.

"The success of our proposal was due, in part, to the paradigm shift we initiated in the epilepsy community in the early 2000s," says Meyerand, who also has an appointment in medical physics. "Until Bruce Hermann (a neurology professor in the UW School of Medicine and Public Health) and I demonstrated that changes in the brain's white matter play an important role in epilepsy, it was thought to be purely a grey matter disorder."

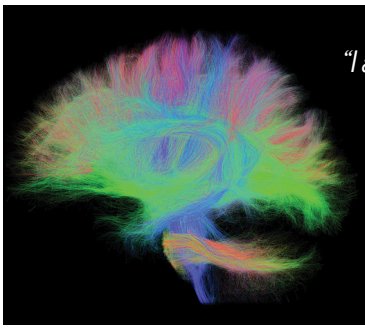
Meyerand compares the brain's grey matter to cities on a map and its white matter to the roads that connect the cities: In a normal brain, these roads are smooth; in an epileptic brain, these roads are bumpy with chipping asphalt. Meyerand and Hermann detected these differences with diffusion tensor imaging—a new technique at the time—which is a special form of magnetic resonance imaging (MRI) that provides pictures of the brain's white matter tracts.

In the NIH-funded epilepsy connectome project, which is completing its second year in fall 2017 and will continue through 2019, Meyerand and colleague Jeffrey Binder, a neurology professor at the Medical College of Wisconsin, are now using MRI and other techniques to map—in unprecedented detail—the brains of 200 healthy adults and 200 adults with temporal lobe epilepsy, the most common form of the disease that affects at least 50 percent of all patients.

Meyerand and Binder are especially motivated by the plight of almost 900,000 American epilepsy patients—35 percent of 2.5 million diagnosed with the disorder—who don't respond to anticonvulsant medications. The next level of treatment for these patients is brain surgery, with a moderate success rate of 40 to 50 percent. Both treatments focus entirely on the brain's grey matter.

"Since the existing treatments don't work for a large percentage of patients, we clearly don't understand the disease well enough yet," says Meyerand. "That's why this research is so important."

Beth Meyerand studies brain maps of epilepsy patients and healthy controls to identify differences in connection patterns that may contribute to the disease.



"I am optimistic that patients will eventually experience much better long-term seizure control than we are able to achieve today."
—Beth Meyerand

For the epilepsy connectome project—the only one of its kind in the world—study participants complete three kinds of MRI scans, provide extensive neuropsychiatric interview data, and (if able to travel to specialized equipment in Milwaukee) undergo magnetoencephalography (MEG) scans.

"The MRI scans provide detailed images of the anatomy, 3D size and connections between different brain regions," Meyerand explains. "As a complementary method, the MEG scans give us real-time measurements of brain activity. Both types of scans are taken while people are resting and relaxing, and also while they perform certain cognitive tasks—for example, memorizing a list of words."

With the scans in hand, Meyerand's team uses computer models to produce color-coded brain maps. Next, the researchers identify potentially meaningful differences in the brain connectome of epilepsy patients and healthy controls with statistical methods. They also examine whether a patient's seizure frequency or response to treatment can be predicted by their baseline MRI or MEG scan results.

The extensive information about the healthy brain's connectome will be a tremendous resource for multiple other research studies going forward: Since the project's data are stored in an NIH-funded data repository, they can be freely downloaded and analyzed by many other researchers, greatly speeding up the rate of scientific discovery, according to Meyerand.

"This project is a perfect example for the kind of big and impactful science that can only be done by a large and highly interdisciplinary research group, in this case representing biomedical engineering, neurology, medical physics, radiology, psychiatry and statistics," Meyerand says. "By targeting epilepsy treatment to each person's unique connectome information—an example of personalized medicine—I am optimistic that patients will eventually experience much better long-term seizure control than we are able to achieve today."

PAYING IT FORWARD:
Ferraro Family Scholarship helps undergrads find—and share—their passion

Hunter Johnson arrived at UW-Madison geared toward the one career he knew would allow him to use his aptitude for science to help others: "In my mind, I was pre-med," he remembers.


Hunter Johnson

However, after a couple of semesters shadowing physicians proved not to be as glamorous as network television promised, Johnson realized that the operating room was not for him. "I started thinking about what my interests were rather than just what I think is a good title," he says. "Applying engineering to life science in BME is where I found my passion."

Johnson, a senior specializing in biomaterials and tissue engineering, has been able to pursue that passion more completely thanks to awards such as the Ferraro Family Scholarship. "The first year of college I had three jobs, the second year I had two," says Johnson. "Having the scholarship allowed me to wholeheartedly get involved in the BME curriculum and undergraduate research."

Alum Rick Ferraro (BSME '79) established the eponymous fund for undergraduate learning in 2003 with the understanding that students have limited time to seize the unique learning opportunities that the university has to offer. "If it weren't for the College of Engineering, I would not be where I am today," Ferraro says. "I'm not obligated to give back, but it's the right thing to do. Where would this world be without engineering?"

"If it weren't for the College of Engineering, I would not be where I am today. I'm not obligated to give back, but it's the right thing to do. Where would this world be without engineering?" *—Rick Ferraro*

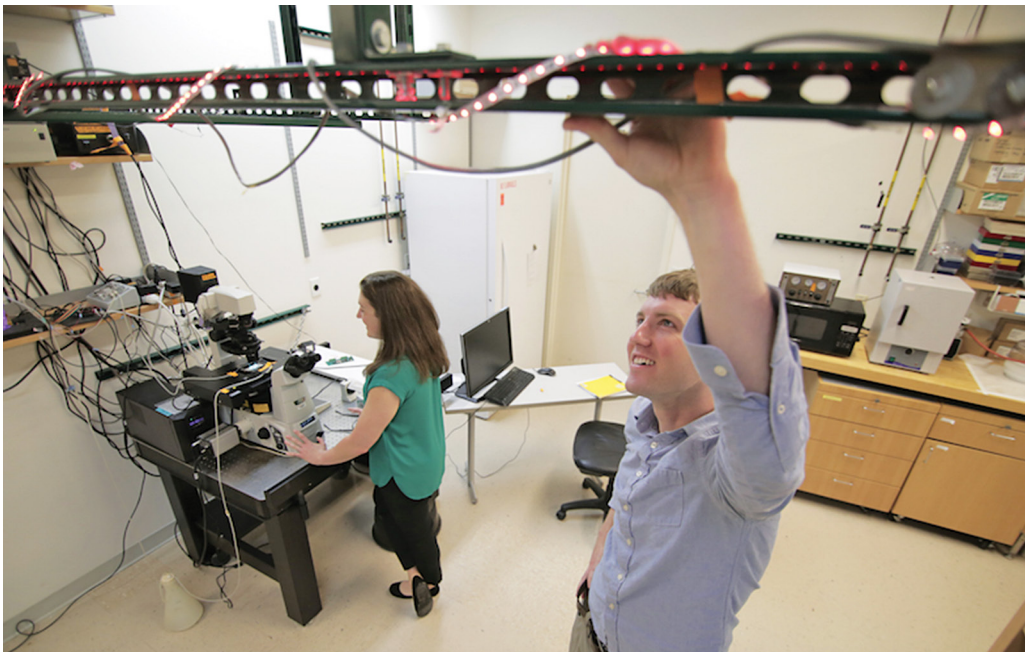
For Johnson, it is not just a question of the hand that engineering has played in forming the world as we know it, but the ways in which engineering can be used to affect positive change going forward. In the past year, he has used the time afforded him by the scholarship to focus on design and research, which he deems the pillars of BME knowledge. He has collaborated on two successful projects in BME's undergraduate design courses; the first, a point-of-care device for malaria detection is now in continued development by Jimma University in Ethiopia. The second, a TAVI (transcather aortic valve implantation) balloon to eliminate the need for pacing the heart in surgery, won an honorable mention for BME 301's Design Excellence Award. Both successes accompany impressive dedication to his research work with the Murphy group. Year-round, he is an undergraduate research assistant for the Brain H-MAPs project—an endeavor seeking to use neural organoids for improved drug toxicity screening and treatment testing.

In summer 2017, he oversaw an independent research project with help from a team of graduate students. He will present his findings in October at the 2017 Biomedical Engineering Society (BMES) annual meeting—an opportunity made possible by his accelerated stem cell education.

With commencement in sight, choosing a graduate school and career are once again on Johnson's mind—but this time, with four years of experience under his belt, he feels confident leaving his options open to exploration in a way high school senior and future "Dr. Johnson" was not. "I can see myself working as a professor, or working in industry, or government research," he says.

Whichever path he chooses to follow, the importance he places on using science to build community is sure to continue—Johnson already pays forward the support shown to him through the Ferraro Scholarship by assisting in the organization of summer science camps at the Discovery Building on campus.

He believes that introducing an interest in STEM fields to disadvantaged and under-represented students will be crucial for the continued growth of biomedicine: "Getting a diverse group in science is necessary. You can't just have one mindset. You have to have different points of view—that's how you can tackle real problems," he says.



Megan McClean and Cameron Stewart have built a novel optogenetic system that monitors light-controlled yeast gene expression. This 'optostat' regulates cellular processes, similar to how a thermostat controls room temperature.

BUILDING A BIOLOGICAL CONTROL SWITCH WITH LIGHT, GENETICS AND ENGINEERING INGENUITY

A user-friendly switch for controlling room temperature, the thermostat is a classic example of the kind of tools engineers build.

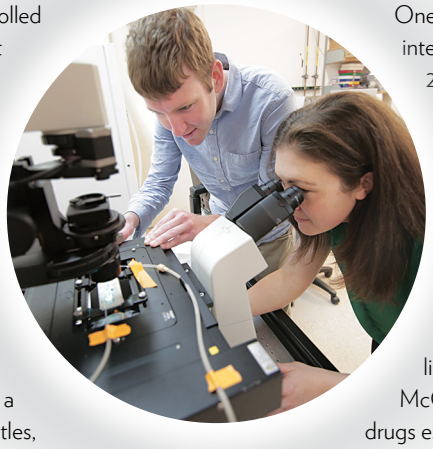
For biological systems research, Assistant Professor Megan McClean and student Cameron Stewart have taken the idea of a thermostat several steps further—and using their invention, which combines the power of light, computers and genetics, researchers can now build an "optostat" that is remarkably similar to the thermostat in our homes. "All you need is three ingredients," says McClean. "An organism that grows well in cell culture, the ability to insert a light-sensitive switch into its genome, and a computer-controlled microscope that images what you want the organism to produce."

The optostat is a fully automated system that connects these three ingredients with electronics and freely available software. Using the light-responsive part of a plant protein to control the expression of a single gene in baker's yeast, the researchers were able to record images of the fluorescent protein produced by that gene continuously for up to 10 days, capturing how the cells responded to the amount of light they received. While light controlled the expression of the gene of interest, it did not affect the transcription of thousands of other yeast genes.

The system contains everything the cells need to grow in excess, except for one limiting nutrient that is provided through controlled release. Like a thermostat, the optostat can automatically adjust the amount of light needed to obtain a desired protein concentration.

Stewart and McClean recently described their optogenetic system in the *Journal of Visualized Experiments*, allowing other researchers—especially biologists without an engineering background—to set it up in their own labs.

Stewart compares their invention to a car's cruise control system. "Cars, throttles, and speedometers already existed, but cruise control combined them with a feedback system," he explains. "In our case, growing cells in a 'chemostat' to maintain a constant growth rate has been possible since the 1950s. But our novel contribution is to connect this chemostat to a light bulb to administer inputs, and to a microscope to measure outputs."



The new optostat is the only system of its kind that can sample and monitor the same cell culture continuously over a long period of time. This allows researchers to study any biological pathway of interest by tuning a single parameter and keeping everything else, including the cells' growth rate, the same.

Optogenetics—the use of light-sensitive proteins as regulators of a variety of cellular processes—has been a growing research field for the last 10 years, McClean says. Since the response of plants to light has been studied extensively, plant-derived proteins make ideal optogenetic tools.

One application of optogenetic systems that McClean is particularly interested in involves *Candida albicans*, the most common of more than 20 species of yeast-like fungi that live in our intestinal tract. They are usually harmless, but their overgrowth can trigger infections in certain body parts, such as the mouth or throat (thrust) and the vagina (yeast infection). When the fungus enters the bloodstream and spreads through the body, it may cause dangerous invasive infections.

Since some *Candida* species tend to form a thin mat, or biofilm, on hip or knee implants and intravenous catheters, they have recently caused severe illness in hospitalized patients and are now considered a global health threat. "Our drug arsenal for fungi is very limited because these organisms are so similar to our own cells," McClean says. "That makes their emerging resistance to antifungal drugs especially disconcerting."

By controlling different regulators of *C. albicans* growth with a light-sensitive switch, McClean hopes to learn what makes the organism change from its stable form in a biofilm—long and skinny—to its less stable, round form that may pop off the biofilm and disperse into the bloodstream. In the future, that knowledge may help inhibit fungal infections in humans without causing toxic side effects.

"One of the unique aspects of fungal biology is its potential to disperse into the bloodstream," McClean says. "In order to study the factors that cause it, we need a controllable system that allows time for a biofilm to form and then make light-induced perturbations. With several modifications we plan to implement next, we believe our optogenetic system will eventually provide that kind of tool."

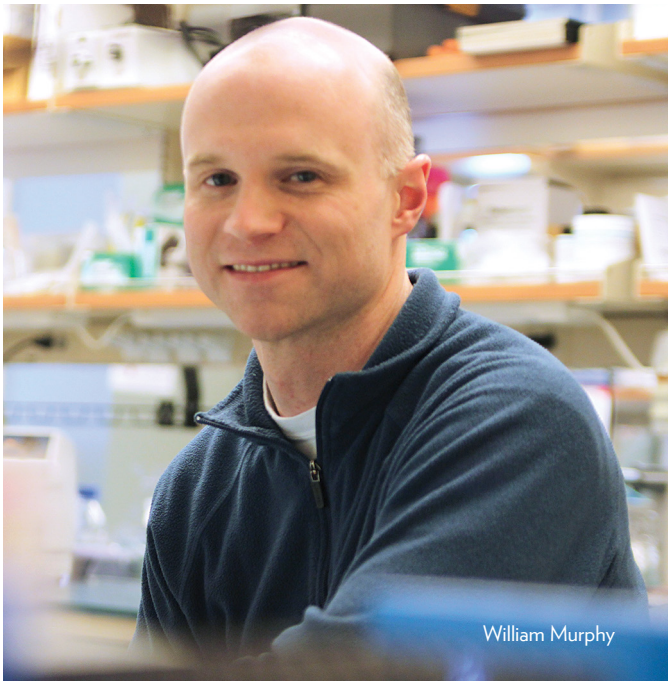
MURPHY TO LEAD GRAINGER INSTITUTE FOR ENGINEERING BIOMANUFACTURING THRUST

A January 2017 article in the journal *Science* called industrial biomanufacturing the future of chemical production. Thus, starting a biomanufacturing thrust within the Grainger Institute for Engineering—an incubator for transdisciplinary research in the College of Engineering—seems timely indeed.

According to thrust lead William Murphy, Harvey D. Spangler Professor of biomedical engineering and orthopedics, and of materials science and engineering, both the time and place may be about as good as it gets. "UW-Madison is well positioned in several ways to be a leader in biomanufacturing," Murphy says. "It is one of the very few places in the world that has large industry players, many emerging startup companies, a broad scope of thought leaders on the academic and industry side, and a major medical center and engineering college co-localized and working actively together."

Dan Thoma, director of the Grainger Institute for Engineering, couldn't agree more. "Bill has shown tremendous leadership in the rapidly growing area of biomanufacturing, and the institute strives to provide support to assist him in achieving his vision for the new thrust."

Murphy's history working with both the private and public sectors will be essential for achieving target outcomes for the program: "For the institute's biomanufacturing thrust, my near-term goals include continuing our engagement with these and other industry partners,



William Murphy

pursuing large-scale funding from federal agencies, and advancing biomanufacturing technologies through transdisciplinary collaboration," Murphy says. "That is consistent with the institute's overarching goal of bridging multiple traditionally distinct engineering departments."

MORE: www.engr.wisc.edu/murphy-lead-grainger-institute-engineerings-biomanufacturing-thrust/

BRAIN BOOT CAMP:
NEW TECHNOLOGY AIMS TO ACCELERATE LEARNING

In today's high-stakes world, where we all need to think, learn or act quickly, the adage "put your thinking cap on" still rings true: Mastering a new task, skill or information often takes the right environment, mindset, sharp focus and lots of hard work, repetition and time. A big boost in learning ability and speed from that proverbial thinking cap would not only be welcome, but critical.

Vilas Distinguished Achievement Professor Justin Williams is leading an effort to create just such a device. With up to $9.85 million in funding from the U.S. Defense Advanced Research Projects Agency. Williams and neuroscience experts from around the country will develop a low-cost, easy-to-use system—think "learning goggles"—that aims to accelerate learning by stimulating nerves in the head and neck to boost neural activity in the brain.

The system will be particularly useful for military personnel—whose safety and our national security depend on their ability to quickly master new skills or digest vast quantities of important information—and for people who have learning disorders or who are afflicted with diseases such as Alzheimer's.

The concept is rooted in a promising new area of research, called targeted neuroplasticity training, in which activating peripheral nerves—those outside of the brain and spinal cord—can promote and strengthen connections of neurons in the brain.

MORE: www.engr.wisc.edu/brain-boot-camp-new-technology-aims-accelerate-learning/

John D. MacArthur Professor & Claude Bernard Professor **David Beebe** received the College of Engineering Byron Bird Award for Excellence in a Research Publication. This prestigious award recognizes a set of seminal publications from Beebe's group in the area of microfluidics.

A research team including Professor **Paul Campagnola** and representatives from the University of Minnesota-Twin Cities and the University of Alabama-Birmingham has developed a new 3D-laser-printed patch that can help heal scarred heart tissue after a heart attack.

Professor **Naomi Chesler** received the college's Equity and Diversity Award—a great recognition of her ongoing efforts and service to the college, department, and university.

Associate Professor **Pam Kreeger** was named a Vilas Associate. This highly competitive, two-year award is selected by the University Research Committee and provides summer salary assistant and flexible funds to support new research directions.

Professor **Kristyn Masters** was one of 13 faculty across campus awarded a Vilas Distinguished Achievement Professorships, an award recognizing distinguished scholarship as well as standout efforts in teaching and service. The professorship provides five years of flexible funding—two-thirds of which is provided by the Office of the Provost through the generosity of the Vilas trustees and one-third provided by the school or college whose dean nominated the winner.

Faculty Associate **Amit Nimukar** *(left)* and Associate Undergraduate Chair **John Puccinelli** *(right)* won Best Paper in the Biomedical Division and a PIC II distinction for their paper on the power of the department's sophomore design course at the 2017 American Society for Engineering Education (ASEE) conference. They will present their findings again next year at ASEE's 125th annual exhibition.

Associate Professor **Melissa Skala** and her collaborator, Associate Professor of Biology Matthew Vander Heiden of MIT's Koch Institute, received a $250,000 Sharp Award at nonprofit organization Stand Up to Cancer's annual 2017 summit for their 250-word proposal of a project focusing on the interactions between tumor cells and healthy cells in pancreatic cancer patients.

STUDENT NEWS

Graduate student **Nicole Piscopo** received a prestigious graduate research fellowship from the National Science Foundation to continue her study of a new leukemia treatment.

TWO NSF CAREER AWARD WINNERS IN 12 MONTHS

The National Science Foundation (NSF) CAREER Award gives promising young engineers the opportunity to explore new technologies and concepts, pushing the boundaries of contemporary science. Between the spring of 2016 and 2017, two department faculty members—Associate Professor Melissa Skala and Assistant Professor Randolph Ashton—were recognized for their achievements.

The $510,00 in funds the award is providing Skala over the next five years will allow her to continue advancing individualized cancer treatment—specifically by building an imaging system that can predict a cancer patient's response to certain types of treatments.

Ashton's award will allow him to create a neural tube—predecessor of a spinal cord—in a dish. The goal of this project is to advance personalized medicine by engineering an easily reproducible platform for biologists to more efficiently study spinal cord diseases; since Ashton will engineer function into the platform, scientists could simply add cells to build a model of whichever spinal cord disease they desire.

Both faculty members plan to use their awards to promote STEM education in their greater communities: Skala previously partnered with schools in Nashville providing inexpensive experimental materials and video conference lab modules to demonstrate various concepts, and she'll continue her outreach with schools in Washington. Ashton will continue outreach initiatives for underrepresented minorities; he has assisted the nonprofit group 100 Black Men of Madison with its K-12 mentoring programs for years and will use the new grant to develop virtual interactive lab experiments and matching teaching modules.

MORE (SKALA): www.engr.wisc.edu/new-biomedical-engineering-faculty-melissa-skala-receives-nsf-career-award/
MORE (ASHTON): www.engr.wisc.edu/human-spinal-cord-tissues-dish-uw-madison-engineer-aims-accelerate-disease-treatment/

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How much information can we extract from a five-minute recording of someone talking? Enough to tell whether that individual may be genetically predisposed to some health complications.

Assistant professor Kris Saha and BME graduate student Arezoo Movaghar are two co-authors of a recent study published in *Scientific Reports* that used machine learning to analyze hundreds of voice recordings and accurately identify individuals with a genetic condition known as fragile X permutation. The condition is characterized by intellectual disability and behavioral, physical and learning challenges; individuals with the condition have an increased risk of developing neurodegenerative disorders, infertility or having a child with fragile X syndrome.

Research on the utility of voice recording analysis in the study of fragile X permutations is not new at UW-Madison—teams from the School of Social Work and the Department of Communication Sciences and Disorders have both demonstrated the valuable insight these recordings provide into diagnosed patients' cognitive and behavioral development. It was the identification of undiagnosed patients, however, that remained problematic—genetic testing and coding speech characteristics from audio recordings to identify fragile X permutations can be time-consuming, resource-intensive, and require clinical expertise. The researchers sought a solution in engineering.

Saha and Movghar are now using machine learning to innovate a legacy of impactful research. "We can go from taking hours to analyze and annotate each recording to needing less than a second," says Saha.

The intial algorithms the researchers developed to distinguish between mothers with and without fragile X permutations have provided results with 81-percent accuracy—taking the first step toward a quicker, more cost-effective screening. According to calculations by the researchers, machine learning-based screening followed by confirmatory genetic tests would save more than $11 million compared to using genetic tests alone to identify 1,000 women with fragile X premutations in the general population.

Machine learning is a form of artificial intelligence by which algorithms are "trained" to analyze new information using existing data. Researchers are using it to identify individuals with a genetic condition known as fragile X premutation. *(Image: Creative Commons)*

Moving forward, the potential for machine learning technology in healthcare is boundless: Movaghar is currently developing a mobile app to streamline data collection from the machine learning algorithms. Saha sees applications for this technology in more than just the diagnosis of fragile X permutations: "What's also exciting is the possibility of using similar algorithms for other disorders," he says.

MORE: www.engr.wisc.edu/machine-learning-can-detect-genetic-disorder-speech-recordings/